Did I hear you second?

DR. SPECTER: I second.

DR. CHARACHE: All right. Let's vote on that.

DR. SPECTER: I am in favor.

DR. CHARACHE: Dr. Reller?

DR. RELLER: Between the two of us, it has been made and seconded, so it's time to vote.

Yes.

DR. TUAZON: Yes.

DR. SANDERS: Yes.

DR. SEEFF: Yes.

DR. WILSON: Yes.

DR. THRUPP: Yes.

DR. CHARACHE: All right. It's also unanimous.

Are there any other conditions? Dr. Thrupp?

DR. THRUPP: At the risk of invoking more discussion--but we have already discussed it, so we shouldn't have to discuss it too much more--I would suggest the recommendation that in addition to the sentence which we have already voted upon that Dr. Reller proposed for addition to the Intended Use paragraph at the very beginning of the package insert, that a third sentence--that is, a second new sentence--be added, that sentence being essentially the second sentence from the top of page 7 about the acute infection limitation, and that sentence might say

for clarity: "A nonreactive antibody test result does not exclude the possibility of exposure to HCV or early acute infection with HCV." Actually, I went to cross out "exposure," because exposure isn't necessarily infection. Let me say it again.

"A nonreactive antibody test result does not exclude the possibility of early acute infection with HCV."

DR. CHARACHE: So it is to delete the word "exposure" and change that to "early acute infection with HCV."

DR. THRUPP: It would leave out "exposure" and be "the possibility of early acute infection with HCV." And I would put that pu in the Intended Use as a caution.

DR. CHARACHE: Okay. Do we have a second?

[No response.]

DR. CHARACHE: Okay. So we will suggest that the FDA consider that sentence and whether it is appropriate, but we don't have a second, so we will not carry it further at this time.

Are there any other recommendations for conditions?

[No response.]

DR. CHARACHE: Okay. Hearing none, we'll call the vote.

So the vote was approval with conditions, and

there were two conditions. The first recommendation was that the statement on the bottom of page 7 be made clear and prominent to indicate the desire of this panel to have confirmatory testing performed with reactive samples in appropriate settings without undue penalty to the manufacturer.

The second was pertaining to wording that indicates that the high-risk patients be divided--after the statement of high-risk patients in Table 5, list the three categories of high-risk patients separately so they can be analyzed, and that there be an indication that emphasizes that this is descriptive of the population studied and not recommendations for specific testing--whatever wording appears appropriate to the FDA and the sponsor.

We'll take a vote on that, and this time, we'll start with Dr. Thrupp.

DR. THRUPP: Yes.

DR. WILSON: Yes.

DR. SEEFF: Yes.

DR. SANDERS: Yes.

DR. TUAZON: Yes.

DR. RELLER: Yes.

DR. SPECTER: Yes.

DR. CHARACHE: So this is unanimous approval with those two conditions, the details to be worked out.

Thank you very much.

Let's go right on now. I think we will probably spent 15 or perhaps 20 minutes on the last item, which is that pertaining to archive samples. If we could put up the questions, let's look at all three questions and then see if we want to answer them separately or whether it is appropriate to address the issues raised without necessarily debating each question.

Dr. Ticehurst?

DR. TICEHURST: While Tom Simms is doing Electricity 101 here, I am probably just as fresh as you all are here, and what I'd like to do is provide a little bit of background on this concept of specimen archives, that actually followed both previous major discussions over the past few days but particularly the one yesterday.

The idea of specimen archives--and I avoided the use of the term "panel" here which is often used, because you guys are a panel, and you get involved in different kinds of panels--so the terminology that is being used here is "specimen archives" to refer to specimens selected for whatever reasons that are then put into a collection and can be pulled back out again.

I'm going to start going through the text of the slides that are going to come up for expediency.

The first principle is that an archive or archives of highly

characterized, well-maintained specimens would be a great advantage to this whole process we are talking about here, the process of evaluating assays for viral hepatitis.

The first point is that they improve the quality of premarket evaluations and improve the quality of package inserts, because the specimens that could go into such an archive can be put in by recognizing the bias that is being used to select to put them in and making that bias as appropriate as possible. And second, by having those as a component of each submission, they enable consistency between submissions; they become an element of each submission. They also become an element that the prospective user can use as a source of comparison between submissions.

The second point is that it reduces the burden on the manufacturer. These become an identified source of appropriate specimens--not "the" identified source but "an" identified source.

May I borrow your pointer, please, Tom?

[Slide.]

So in our collective stupor here, I have already addressed the first several bullets, and now I am onto the last one here, and actually, I have already addressed that one. At least in terms of these specimens, there is less data for them to generate and prepare, because the

characteristics of these specimens are already known.

DR. SEEFF: John, is this your effort at FDA?

DR. TICEHURST: I think I will answer your question by continuing, Dr. Seeff. Thank you.

[Slide.]

Within the Microbiology Branch, we have had a long history of recommending such archives to certain other microorganisms, in particular, assays for antibodies for borrelia bergdorferi [ph.] and assays for antibodies to herpes simplex viruses.

At a previous meeting of this panel a little less than two years ago, this whole concept came up a number of times as a suggestion and an approach to coupling two factors. One was the need for data from appropriate specimens--again, this goes back to the kinds of discussions that were held yesterday and today--including serially collected specimens, coupling that with the difficulties in obtaining these specimens, either prospectively or from other sources in a retrospective forum.

As I mentioned in my comments this morning, we repeatedly hear from the manufacturers that they have a very difficult time in any way, not even just in a cost way, of obtaining these appropriate specimens, particularly if they represent serially collected specimens.

[Slide.]

Hopefully, Dr. Seeff, this addresses your question. Those of us in the Microbiology Branch have been actively seeking the development of such specimen archives a this point via discussions with other groups within the Department of Health and Human Services, several agencies within DHHS, and also through a number of discussions and by collecting information from companies that collect, maintain and sell such specimens. You heard from one such company yesterday. I would mention that at this point in time, we do not regulate these companies. These specimens are sold without FDA oversight.

[Slide.]

There are a lot of technical issues that relate to these specimens, and I am talking about the integrity of the specimens once they have been selected that I am sure you are all familiar with that have to do with do you aliquot them, how do you aliquot them, how do you maintain them, alarms on freezers, what are the criteria to keep them and so forth. These basically are quality control and quality assurance issues, but one in particular that probably would have been more apparent yesterday was to deal with the recognized liability of IgM antibodies, and this, of course, would pertain to IgM anti-HCV and would also potentially pertain to IgM anti-HAV, and in the event that any similar assay was developed for HCV at some point, and considering

other hepatitis viruses that might come down the line as well, like HEV, for example.

That was the background. Now, the questions, which I am not the author of but the messenger, but I will try to put some context with them, are as follows. Will the use of characterized viral hepatitis archives provide assurance of assay safety and effectiveness in various populations? To try to clarify this a little bit, what this question is asking, which may have an obvious answer, is: Is this a good idea?

The second part of it that might not be clear is "various populations." In general, I think those would refer to populations that would pertain to well-recognized or potential indications for use. So if we could take some of the discussion today, such a population might be a population of acute HCV infections and so forth.

[Slide.]

What criteria should be used to include specimens in these archives? I think that here, the word "criteria" can be a very loaded term. In general, I think this could refer to the information about the specimens. It could include things like clinical background, other laboratory data, results from reference assays, results from a consensus of reference assay testing. Other criteria could be deciding how to prioritize which specimens are the most

important first. Would it be more important, for example, if you are thinking about HCV, to have well-characterized specimens representing chronic HCV versus those representing acute HCV? If you are going to have specimens representing the indication for anti-HBS assays of assessing unity post-vaccination, what kinds of criteria would be used to select those, and so forth? How stringent should those criteria be? We have had discussions both yesterday and today about stringent criteria versus less stringent criteria. And obviously, these criteria would depend on the purpose of a given group of specimens.

Finally, the last question, which to me seems a lot like the first one: Will archives be sufficient to support claims for a diagnosis of HBV infection--I think this could be substituted with any of the five known viruses at this point in time--A, B, C, D, and E--or immunity in all indicated populations. I think that where this differs from the first question is what other kinds of things might be needed, and as a specific point, what are the advantages that fresh, not previously frozen specimens provide that would not be encompassed in an archive?

Thank you.

DR. CHARACHE: Thank you.

Let's put up the first question.

Dr. Thrupp?

DR. THRUPP: As a matter of background information, you indicated that your division of the FDA has been using archive specimens in evaluating previous other devices, other serologic tests. Do you have any experience that could be related from those previous archive specimens that would indicate that they were misleading? For example, were they too circumscribed and too limited a group that when you got into the field experience, there were errors or problems that were not predicted by the archived sampling, or where the archives turned out to be inadequate or poorly defined, or have they in fact been very helpful, and you haven't had any problems with the archives?

DR. TICEHURST: I'm not going to give you a great answer to that question. I am not familiar with the characteristics of the anti-HSV's archives, and I think there are some people who might be able to address that better than I if they would like to.

I have dealt directly with data from the archives that pertain to anti-borrelia [ph.], and I think that that's a good example to consider. I haven't looked at data from recent submissions, so I am reflecting on things that I did a couple of years ago.

Part of the problem there is, as many of you know, that it is very difficult, short of having culture or perhaps detecting borrelia DNA to come up with--I'm sorry--

it is relatively easy to come up with people who meet strict criteria for an acute borrelia infection. I'm speaking particularly here about borrelia bergdorferi. It is more difficult to come up with criteria for people who meet strict criteria for a chronic bergdorferi infection. It is pretty easy to come up with a lot of people who meet somebody's criteria for bergdorferi infections, because there are things involved with rashes and so forth and so on.

The particular collections that I am referring to are maintained at CDC and are made available, and generally, our branch insists that the manufacturer of an anti-borrelia assay use those specimens, and they provide very useful information, but there are a lot of limitations in that information.

DR. CHARACHE: Okay. I think maybe we can move this along a little bit with the first question. I wonder if the group might feel that the characterized viral hepatitis archives could provide assistance--this isn't saying yet whether it is the only thing you need or not--in various populations if the archive has been appropriately clarified and designated in terms of collection of information required and has been collected and stored in a manner that is appropriate to preserving the factors that you are trying to assay.

Would that perhaps summarize Question 1?

DR. THRUPP: Amen.

DR. CHARACHE: Yes?

DR. EDELSTEIN: I think that there are a number of broad issues. One, I don't think that we as a panel can give expert advice as far as what specific populations should be considered for an archive. My suggestion would be to convene a special panel of hepatologists in this case for that.

What I would be concerned about from the laboratory standpoint is that there are several things you have to consider. One is will there be specific effects on certain matrices with storage that you can't predict until you run it; so you are always going to need some means of backing up your archival specimens with fresh specimens to determine that there is no adverse effect of storage on certain matrices or certain methods of analysis.

The second restraint that you have is you have to make certain that in your defined populations, they are not so polar that you exclude the patients who have close to equivocal results, because those are the most valuable for determining the true performance of the assay. If you have people who would have, let's say, assay values of 5,000 or assay values of 5, that is useful, but you also need another population where you have some equivocal range values to

help you out.

DR. CHARACHE: All right. We have now listed four requirements to make this safe and effective for use. The first is appropriate clinical information, and we haven't defined what that is. The second is appropriate collection and storage and aliquoting and so on, handling of the sample. Third is documentation that there are no matrix effects that would adversely affect it. And fourth is that the populations not be so polar, not so yes-and-no, that you can't pick up the key information at the break point or in the middle somewhere.

Are there any other factors we would like to address?

DR. EDELSTEIN: I'm sorry--there is one more in that we have seen over the last two days that sometimes, knowing as much about the patient as possible is very helpful in trying to interpret a result. So if there were some way of getting archival information that would include follow-up, clinical data, from the time the specimen was drawn, plus retrospective information prior to the time the sample is drawn, that would be of real important or could be of real importance.

DR. CHARACHE: Dr. Seeff?

DR. SEEFF: Archive specimens are extremely important. Anything that I personally have ever done has

come out of archive specimens going back 50 years. So I think the existence of archive specimens is very important. I know, for example, that NHLBI has a large repository with a committee on which I happen to serve, but these are being collected through studies that NHLBI has supported.

NIDDK is now thinking of setting up a repository. This is slightly different. This is for the purpose of supporting, presumably, companies who many need to have identified samples.

One problem we face is linkage and the problem of having specimens and wanting to go back and do tests on individuals for whom you don't have permission. I am facing that now in a couple of studies, and it's a real problem, how to go about it. I suppose, if you are going to develop a new set of samples by drawing blood from people now with acute hepatitis or chronic hepatitis or whatever form of liver disease you want, I suppose you could have a consent form which says we are drawing blood specifically for this purpose, and the purpose of this is to go back and test it, and we may want to do a whole variety of tests over the next 25 or 50 years as new things become available, and if they consent to that, then I guess that might be fine. But otherwise, the problem of testing and linking--and I think linkage is very important; I agree with what was discussed, that without knowing the clinical circumstances--and also,

follow-up is extremely useful--it loses part of its usefulness.

So I think this is an issue that we need to be very cautious about, and you and I touched on it when we discussed this in the car, that maybe this is an issue that has to be raised.

DR. CHARACHE: Are there any other comments on Question 1?

DR. NOLTE: We're not talking about replacing fresh clinical specimens with archived; we're talking about using them to supplement--correct?

DR. CHARACHE: That's what this one is. We'll come to another--

DR. GUTMAN: Well, actually, it depends on whether you decide to rewrite "assist" versus "assurance". There is an implication here--and actually, this has implications beyond viral hepatitis, because we will be studying diseases in the future, perhaps genetic markers where prospective studies can't be done, and we may need to look at some kind of banking samples. So it really has very broad implications.

I don't mean to be provocative or leading, especially late on a Friday, but I will--the deal here was that yesterday, we had a product before the panel--I wouldn't wish to suggest that the panel is required to be

any more or less consistent than the FDA--but we had a product before the panel which was based very heavily on archived samples, and the issue that I actually asked the panel about wasn't whether it was okay to use archive samples or not. I thought the issue was where they characterized appropriately with appropriate follow-up or lack of follow-up; did they have the stability issues resolved. Yesterday's may or may not have had them resolved. Had they been stored correctly; were there representative populations or biased populations.

Assuming we could deal with that with B or C or D or E or F or G or whatever, assuming we could deal with this, would you be comfortable if we came through and essentially maybe had fresh samples on some donors and had our disease characterized with archive samples? Is that established for a well-established marker for B, but not for a new marker like E or G, or something else?

DR. THRUPP: That gets to Question 3, which essentially asks are the panels enough by themselves, or what else do you need.

DR. CHARACHE: Yes. I think that was what I was thinking. I guess, though, this is a point--this says "provide assurance of safety and efficacy," and I was reading it as "provide assistance"; so I think we've been talking about it as assistance, and we'll get to 3, and

we'll say "assurance".

Yes, Dr. Gates?

DR. GATES: Kind of to Steve's point, it seems to me that given the caveats in terms of the characterization and everything, that if that's true, there is no real advantage in prospective studies if you have archive samples like this in addition, that archive samples have an additional advantage in that you can basically standardize tests across different products. It has been done in the past for susceptibility testing and stuff like that, with resistance panels. You can start getting a real good idea of how one test compares to another test because you're using the same set of standards.

So to my mind, it seems like there are advantages here and not any real disadvantages.

DR. CHARACHE: Dr. Wilson?

DR. WILSON: There are clearly advantages to having pools of well-characterized, properly stored sera for the reasons that have been given. But on the other hand, what are these products going to be used to test in the real world? People just don't collect blood. I mean, you can collect serum in one of several different ways. There is a movement going on in this country with these pediatric tubes for adults. We found that clearly, those don't behave the way adult tapes do. So there are a lot of factors that are

only going to come out in clinical trials.

So I think that relying on these solely as the basis upon which to make a decision would be wrong. I think you still need to have prospective clinical trials to ferret out how things work in the real world.

DR. CHARACHE: Other comments?

Dr. Nolte?

DR. NOLTE: I think that clearly today we saw a good example of how well-characterized panels could be meshed with prospectively collected specimens to give a more or less efficient clinical trial of the product. So I don't know exactly whom I agree with, but certainly, in my mind, I'm not thinking about replacing a clinical trial with a well-characterized archive panel. There has got to be a component of that if what you are trying to approve is a diagnostic test that is going to be used in a clinical laboratory. They are complementary, clearly.

DR. CHARACHE: Yes. I think, reinforcing what Dr. Nolte has said, there was 100 percent specificity in the archive samples that we were hearing about today, and a 20 percent specificity in the ones that were tested in real time. The populations weren't the same, but I think this also helps emphasize one of the points that Dr. Edelstein made about not having a polar population and ensuring also that there are no matrix effects and so on.

Can we look at Number 2 and see if we have anything further to add? "What criteria should be used to include specimens in these archives?"

I am going to suggest that it depends on what they are to be used for. Is there anyone who would like to say more than that?

DR. NOLTE: Someone suggested earlier that it is going to be a panel on hepatitis, and what we are focused on are clinical criteria. Maybe we ought to convene a panel of hepatologists to make that designation.

DR. CHARACHE: But I am also going to suggest that there be criteria for the size of aliquots--in other words, you might have a few large ones that are then thawed and refrozen only once and put into small tubes--and that there be the same type of rigid monitoring of processing and equipment that we have for laboratory monitoring of process and equipment, if not more stringent, because there are going to be used to establish laboratory practices. So there should be alarms on the freezers; there should be the appropriate freezer temperature; there should be appropriate processing of the samples that are originally achieved. And if they are collected through phlebotomy, as in a plasmapheresis center, there needs to be very careful understanding of the anticoagulant effects and the decreased amounts of calcium and all this kind of thing on the

persistence of the factors you want to measure.

DR. SPECTER: I think you have to well-define the source, too, that they come from, either via some kind of gold standard test, or if there is no such thing, one or more reference tests, to assure that you have a positive or a negative, that the individual has a particular condition or not, or what other conditions the source may have had. So trying to define the source as well as possible would be very important.

DR. CHARACHE: Other recommendations? I think this would need to be fleshed out on a test-by-test basis to some extent. There are some that are global.

Number 3. Dr. Stewart, did you want to add something?

DR. STEWART: I was just going to say we have used both lyophilized serum specimens and the whole frozen specimens, and the problem we ran into about 20 years ago was that our rubber stoppers for our lyophilized specimens were not really air-tight or waterproof, and after about 10 years, we had bricks in our tube instead of something that would reconstitute. Yet in many ways, if the procedures of lyophilization have improved, you can be much more sure of the stability of your product.

DR. CHARACHE: Thank you.

The last question: "Will archive be sufficient to

support the claims of diagnosis of HBV infection or immunity for all indicated populations?"

MR. REYNOLDS: That's going to depend on the specimens.

DR. CHARACHE: Okay.

DR. THRUPP: Well, I think the intent of that question is the point that has already been made many times, that yes, the archived panels will provide primarily guidelines in important areas, but no, you still have to have samples from the real world in order to validate the assay in real time.

DR. CHARACHE: Any other comments?

[No response.]

DR. CHARACHE: I think the panel strongly supports the use of appropriate archive samples, but would like to ensure their comparability to what is going to be seen.

I believe this finishes our business. I would like to thank the panel for hanging in there and for some hard work and thank the FDA for their support.

MS. POOLE: And I'd like to again thank Dr. Charache; she has been a voting member for four years, before that a consultant, and if she so desires, she will stay on as a consultant to the panel.

Dr. Gates, we are truly sad to see you go, and whenever you see the announcement in the future, feel free

to apply again. Thank you.

And thank you, Dr. Nolte, our guest, and thank you, Dr. Seeff, and everybody else for coming.

DR. CHARACHE: Thank you. I would particularly like to thank Freddie for keeping me alive for four years.

[Applause.]

[Whereupon, at 3:45 p.m., the proceedings were concluded.]

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CERTIFICATE

I, ANNIE HAYES the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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